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Effect of Lidocaine and Bretylium on Energy Requirements for Transthoracic Defibrillation: Experimental Studies

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The purpose of this study was to determine the effect of the antiarrhythmic drugs lidocaine and bretylium on the minimal energy requirement for transthoracic defibrillation—the defibrillation threshold. Closed chest dogs were anesthetized with chloralose or pentobarbital; lidocaine was administered at varying rates for 2 hours and defibrillation threshold periodically redetermined. Similar protocols were followed for bretylium. Serum lidocaine levels from therapeutic to toxic ranges were obtained, and up to a 60% ($p < 0.05$) increase in defibrillation threshold in the pentobarbital-anesthetized dogs was demonstrated. In chloralose-anesthetized dogs the lidocaine effect was modest, with only a 10 to 20% rise in defibrillation threshold (p = NS) despite similar increases in serum lidocaine levels.

Thus, lidocaine increases the minimal energy requirements for transthoracic defibrillation, but this effect is in part anesthesia-related, indicating a lidocaine-pentobarbital interaction. When phentolamine was administered to chloralose-anesthetized dogs receiving lidocaine, defibrillation threshold rose 13% ($p < 0.05$); this suggests that alpha-adrenergic receptor blockade is at least in part the mechanism of the pentobarbital-lidocaine interaction on defibrillation threshold. Bretylium with either anesthetic had no significant effect on defibrillation threshold.

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The antiarrhythmic drugs lidocaine and bretylium are widely administered to prevent or treat ventricular arrhythmias, usually in the setting of an acute myocardial infarction or other serious cardiac illness. Because these drugs are not completely effective, however, some patients inevitably develop ventricular fibrillation despite the drugs and require immediate direct current countershock for defibrillation. Thus, many patients undergoing defibrillation have recently received or are receiving lidocaine or bretylium.

Two recent experimental studies (1,2) found that antiarrhythmic agents affected the minimal energy required for transthoracic defibrillation: lidocaine increased energy requirements and bretylium decreased them. If these results are reproducible and apply to humans, they suggest that patients who develop ventricular fibrillation while receiving lidocaine will require transthoracic shocks of higher energies to achieve defibrillation, whereas patients receiving bretylium may require less energy than usual to defibrillate. However, these studies (1,2) were performed on small groups of dogs, only a single anesthetic was used and no plasma drug levels were reported to correlate with the effects on energy requirements. Furthermore, a recent study (3) could not demonstrate an effect of bretylium on defibrillation energy requirements. Because of these conflicting but potentially important experimental observations, our purpose in this study was to assess the reproducibility of the earlier defibrillation observations in a larger number of animals, to correlate the effect of lidocaine on transthoracic defibrillation energy requirements with plasma levels and to determine whether the anesthetic agent used in the experiment would affect the results.

Methods

Experimental preparation. Mongrel dogs weighing 15 to 25 kg were used. The dogs were anesthetized with either intravenous chloralose (100 mg/kg body weight) and urethane (1,000 mg/kg) or intravenous pentobarbital (15 mg/kg);

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supplemental anesthesia was given as necessary. The animals were intubated and ventilated using inspired room air with supplemental oxygen as necessary. Arterial blood gases were determined every 30 minutes and intravenous sodium bicarbonate was given or the ventilation rate was adjusted as necessary to maintain the pH and partial pressure of carbon dioxide (P_{CO_2}) in a physiologic range. Polyurethane 8F catheters were inserted into the brachial artery and passed retrograde to the left ventricle from pressure monitoring. Heart rate was determined from an external electrocardiogram.

Ventricular defibrillation threshold. Defibrillation threshold, the minimal shock energy required to defibrillate the heart during each of the conditions assessed, was determined using a modification of the technique of Babbs et al. (4). A bipolar catheter was passed to the right ventricular apex, and ventricular fibrillation was initiated by delivering a 60 Hz, 2 to 10 V, 5 second duration train of rectangular electrical pulses by way of the catheter. Ventricular fibrillation was allowed to persist for 15 seconds. We then administered an initial shock of 160 J (energy delivered into a standard 50 Ω resistance), which is adequate to defibrillate most dogs weighing 15 to 25 kg. All shocks were given from electrode paddles placed over the cardiac apex on the shaved left chest and the corresponding location on the shaved right chest. Hewlett-Packard Redux paste, a low resistance electrode gel, was used as the electrode-skin interface in all cases. The electrode paddles were held against the chest by a mechanical holding device that ensured a constant electrode paddle position and a constant electrode paddle pressure against the chest. This fibrillation-defibrillation sequence was repeated at 3 minute intervals, with the shock energy decreased in 20 J decrements: 160 J, 140 J, and so forth. When a shock failed to defibrillate, the energy was immediately increased by 10 J and the shock was repeated. If necessary, another shock, 10 J higher, was quickly given.

The defibrillation threshold was defined as the lowest energy shock resulting in defibrillation; its reproducibility was ensured by immediately repeating the determination at the last two energy levels, starting at the previous highest energy level that failed to defibrillate and then immediately raising the shock energy to the previous successful level. Babbs et al. (4,5) showed that such fibrillation-defibrillation episodes were well tolerated by anesthetized dogs and did not in themselves cause blood gas changes or other physiologic abnormalities.

All shocks were administered using 8 cm diameter electrode paddles and a Mennen-Greatbatch Cardiosentinal direct current defibrillator, which delivers a damped sinusoidal waveform. The nominal delivered energy dial settings on the defibrillator were checked for accuracy before the study by discharging the defibrillator into a Dynatech Nevada defibrillator analyzer (model PEI 3100A).

Antiarrhythmic Drugs

After determination of control defibrillation threshold, lidocaine or bretylium was administered and defibrillation threshold was redetermined every 30 minutes for 2 hours.

Lidocaine. To achieve a wide range of serum lidocaine levels and to correlate these levels with changes in defibrillation energy requirements we varied the initial bolus dose and subsequent rate of lidocaine infusion. An initial group of 16 chloralose-anesthetized dogs received low dose lidocaine: an intravenous bolus dose of 4 mg/kg, followed by an intravenous infusion of 0.1 mg/kg per min for the first hour and 0.2 mg/kg per min for the second hour. This dose was chosen to yield serum lidocaine levels in the low therapeutic range. In another group of six chloralose-anesthetized dogs, we administered high dose lidocaine: an initial 10 mg/kg intravenous bolus, followed by intravenous infusions of 0.3 mg/kg per min for the first hour and 0.6 mg/kg per min for the second hour. This was done to deliberately achieve serum concentrations in the high therapeutic and toxic ranges. In nine pentobarbital-anesthetized dogs an intermediate lidocaine dosage schedule was used: a bolus dose of 4 mg/kg, followed by infusion rates of 0.2 mg/kg per min (first hour) and 0.4 mg/kg per min (second hour). This different dose was selected to achieve a wider spectrum of increasing lidocaine concentrations from the therapeutic to the toxic range, while decreasing the total number of animals required to achieve this spectrum of different serum levels. We subsequently found that this intermediate dose lidocaine schedule yielded lidocaine levels that even after only 30 minutes of infusion were in the high therapeutic to toxic range. Therefore, we studied two additional dogs using a very low dose lidocaine schedule: an initial bolus of 2 mg/kg, followed by an infusion rate of 0.1 mg/kg per min for 30 minutes, at which point defibrillation threshold was remeasured. This was intended to yield lidocaine concentrations in the low therapeutic range.

Plasma lidocaine concentrations were determined using a homogeneous enzyme immunoassay, which correlates well with measurements by gas liquid chromatography (6). This assay does not determine metabolites of lidocaine (6,7).

Bretylium. Both chloralose- and pentobarbital-anesthetized dogs ($n = 10$ and $n = 10$, respectively) received an initial intravenous bolus dose of bretylium tosylate, 5 mg/kg intravenously, and this dose was repeated 1 hour later. Determinations of plasma or myocardial bretylium levels were not available to us at the time of this study, despite attempts to obtain such determinations.

Additional Studies

Mechanisms of lidocaine-pentobarbital interactions. In our preliminary studies (8) we found that the effect of lidocaine on defibrillation threshold was much greater in pentobarbital-anesthetized dogs than in chloralose-anesthe-

tized dogs, an effect that was not explained by differences in serum lidocaine levels. We hypothesized that the mechanism of this apparent interaction between lidocaine and the barbiturate might be in the known but complex effects of barbiturate anesthesia on sympathetic and parasympathetic activity (9,10). We therefore sought to mimic such effects by administering lidocaine to chloralose-anesthetized dogs, determining defibrillation threshold, then undertaking additional interventions and redetermining defibrillation threshold. If any of these additional interventions were the mechanism of the lidocaine-pentobarbital intervention, the defibrillation threshold in chloralose-anesthetized dogs receiving the additional intervention should have risen markedly, simulating the effect of lidocaine in the barbiturate-anesthetized dogs.

Role of beta-receptor activation or blockade. First, we evaluated the possibility that the interaction might involve beta-adrenergic receptor activation or beta-adrenergic receptor blockade. In two dogs anesthetized with chloralose, we determined control defibrillation threshold, administered lidocaine according to the high dose protocol and redetermined defibrillation threshold after 1 hour of lidocaine administration. With the lidocaine infusion continuing, we then added an intravenous infusion of the beta-adrenergic receptor agonist isoproterenol to increase the heart rate by at least 25%. After 15 minutes of isoproterenol administration, we redetermined defibrillation threshold. This demonstrated the effect of beta-adrenergic receptor activation. Then with isoproterenol and lidocaine still being infused, we administered the beta-adrenergic receptor antagonist propranolol (2 mg intravenously); complete beta-adrenergic receptor blockade was first verified by a propranolol-induced decrease in heart rate to pre-isoproterenol levels. We then discontinued the isoproterenol infusion and waited an additional 15 minutes for heart rate and blood pressure to restabilize at a level reflecting the effect of the beta-adrenergic receptor blockade. We then redetermined defibrillation threshold. This indicated the effect of beta-adrenergic receptor blockade.

Role of alpha-adrenergic receptor activation or blockade. Second, we evaluated the possibility that the pentobarbital-lidocaine interaction might involve alpha-adrenergic receptor activation or blockade. In two additional dogs anesthetized with chloralose, after 1 hour of high dose lid ocaine administration and determination of its effect on defibrillation threshold, we added the alpha-adrenergic receptor agonist phenylephrine, at a rate of 0.15 mg/min intravenously, to increase the systolic arterial pressure by at least 25%. After 15 minutes of phenylephrine and lidocaine administration we redetermined defibrillation threshold. This demonstrated the effect of alpha-adrenergic receptor activation. In six chloralose-anesthetized dogs we determined the effect of the alpha-antagonist phentolamine. In these six chloralose-anesthetized dogs we administered high dose lidocaine for 1 hour and determined its effect on defibrillation threshold. We then administered phentolamine at 0.25 to 0.5 mg/min to reduce the systolic arterial pressure by at least 25%. After 15 minutes of phentolamine and lidocaine administration, we redetermined the defibrillation threshold. This indicated the effect of the alpha-adrenergic receptor blockade on defibrillation threshold of chloralose-anesthetized dogs receiving lidocaine. To be sure that the observed effect of phentolamine plus lidocaine on defibrillation threshold was not simply a nonspecific effect of phentolamine completely unrelated to the anesthesia, we also administered this drug to two *pentobarbital*-anesthetized dogs receiving high dose lidocaine (0.6 mg/kg per min) to cause a 25% decrease in systolic blood pressure, and then redetermined defibrillation threshold.

Role of cholinergic or anticholinergic effect of pentobarbital. Third, we evaluated the possibility that the lidocaine-pentobarbital interaction might be explained by a cholinergic or anticholinergic effect of the barbiturate. In three chloralose-anesthetized dogs we exposed the vagi by blunt dissection bilaterally. A midcervical vagotomy was performed and electrodes were attached to the distal vagi. Stimulation was performed using a Grass stimulator that delivered 1.5 mA of current at 20 Hz, with 4 ms pulses. The end point was a decrease in heart rate of at least 25%. Defibrillation threshold was then redetermined. In two additional chloralose-anesthetized dogs we administered high dose lidocaine and determined defibrillation threshold after 1 hour. With lidocaine still being infused, we then administered atropine, 2 mg intravenously; cholinergic blockade was verified by a heart rate increase of at least 25%. We then redetermined defibrillation threshold.

Role of drug effect on transthoracic impedance. Finally, we examined the possibility that the effect of lidocaine and pentobarbital on defibrillation threshold might be related to an effect of either or both of these drugs on transthoracic impedance. If impedance was markedly reduced by these drugs, less energy would be required to achieve the minimal current needed to defibrillate; thus, defibrillation threshold would be reduced. To evaluate this we anesthetized two dogs with Innovar Vet (fentanyl droperidol), 0.13 ml/kg. Shocks of 70 J were given to these animals using a Hewlett-Packard model 78670A defibrillator, which annotates peak current and transthoracic impedance after each shock. Each animal received an initial pre-control shock; data from this first shock were discarded, because it has been shown that transthoracic impedance tends to fall with repeated shocks, but particularly after the first shock (11,12). We then administered two control shocks separated by 5 minutes and followed by an infusion of pentobarbital, 15 mg/kg intravenously. After 15 minutes, two more shocks were given 5 minutes apart. Then the animals received lidocaine according to the intermediate dose pentobarbital procotol: a 4 mg/kg intravenous bolus, followed by a lidocaine infusion,

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0.2 mg/kg per min for 30 minutes, and two final shocks 5 minutes apart. After each shock transthoracic impedance was noted.

Statistical analysis. Multiple comparisons of drug effects on hemodynamic variables and defibrillation thresholds were made by analysis of variance for a repeated measures design. Paired comparisons (in the studies of the lidocaine-pentobarbital interaction mechanism) were done using Student's *t* test. All data are expressed as mean ± 1 standard deviation (SD).

Results

Lidocaine (Table 1). Sixteen dogs received chloralose anesthesia and low dose lidocaine, six received chloralose and high dose lidocaine and nine received pentobarbital and intermediate dose lidocaine. The serum lidocaine concentration achieved by lidocaine administration in the three lidocaine protocols used are shown in Figure 1. The effects of lidocaine on left ventricular and aortic pressures, heart rate and defibrillation threshold are given in Table 1. The defibrillation thresholds varied markedly in individual animals, ranging from 20 to 200 J. The standard deviation within each group was large and there was considerable variation among groups. For comparative purposes we therefore also normalized the defibrillation thresholds by dividing each individual dog's defibrillation threshold determined during drug administration by that dog's control threshold. A similar procedure was used by Babbs et al. (4). These data are shown in Figures 2 and 3.

Lidocaine caused no significant hemodynamic changes in any of the three dosage schedules used. Maximal serum lidocaine concentrations achieved were 3.8 ± 0.8 μg/ml (± SD) (chloralose anesthesia, low dose lidocaine administration), 15.0 ± 3.6 μg/ml (pentobarbital anesthesia, in-

Table 1. Effect of Intravenous Lidocaine on Hemodynamics and Defibrillation Threshold

		Lidocaine			
	Control	30 Min	60 Min	90 Min	120 Min
A. Chloralose Anesthesia, Low Dose Lidocaine Infusion Protocol (n = 16)					
Heart rate (beats/min)	196 ± 28	192 ± 25	184 ± 21	188 ± 30	191 ± 30
Systolic arterial pressure (mm Hg)	167 ± 31	148 ± 24	146 ± 22	149 ± 20	153 ± 23
Diastolic arterial pressure (mm Hg)	104 ± 21	96 ± 16	95 ± 13	96 ± 14	98 ± 18
Left ventricular end-diastolic pressure (mm Hg)	7 ± 2	7 ± 3	8 ± 4	8 ± 3	7 ± 2
Serum lidocaine (μg/ml)	0.1 ± 0.1	2.2 ± 0.7	2.4 ± 0.7	3.4 ± 0.9	3.8 ± 0.8
Defibrillation threshold (J)	79 ± 30	82 ± 32	84 ± 38	90 ± 46	90 ± 49
B. Chloralose Anesthesia, High Dose Lidocaine Infusion Protocol (n = 6)					
Heart rate (beats/min)	190 ± 31	175 ± 33	156 ± 28	137 ± 21	—
Systolic arterial pressure (mm Hg)	174 ± 8	159 ± 12	151 ± 5	147 ± 3	—
Diastolic arterial pressure (mm Hg)	100 ± 8	99 ± 14	101 ± 5	98 ± 3	—
Left ventricular end-diastolic pressure (mm Hg)	7 ± 1	8 ± 1	8 ± 2	9 ± 3	—
Serum lidocaine (μg/ml)	0.0 ± 0 1	8.0 ± 2.1	9.2 ± 1.0	14.1 ± 2.4	16.6 ± 4.9*
Defibrillation threshold (J)	119 ± 50	130 ± 59	120 ± 83	143 ± 121	—
C. Pentobarbital Anesthesia, Intermediate Dose Lidocaine Infusion Protocol (n = 9)					
Heart rate (beats/min)	180 ± 18	178 ± 14	171 ± 20	164 ± 25	164 ± 29
Systolic arterial pressure (mm Hg)	153 ± 22	150 ± 21	143 ± 14	132 ± 14	129 ± 13
Diastolic arterial pressure (mm Hg)	112 ± 14	108 ± 16	106 ± 12	98 ± 12	96 ± 14
Left ventricular end-diastolic pressure (mm Hg)	11 ± 4	12 ± 3	13 ± 3	14 ± 3	14 ± 3
Serum lidocaine (μg/ml)	0.2 ± 0.2	6.2 ± 1.5	7.6 ± 2.5	12.8 ± 2.9	15 0 ± 3.6
Defibrillation threshold (J)	49 ± 20	64 ± 27	68 ± 37	77 ± 32	78 ± 36

*Only two dogs in this subgroup survived at 120 minutes. All data are expressed as mean ± SD.

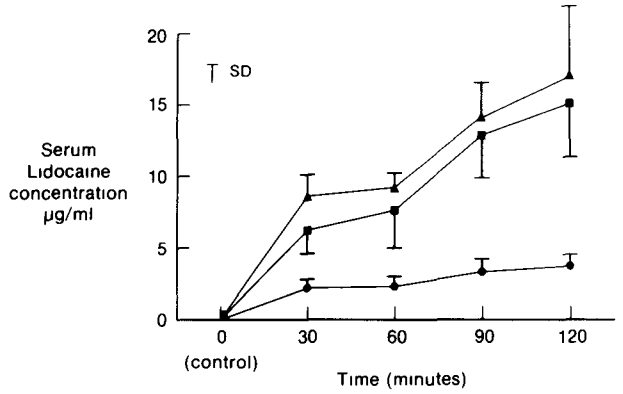
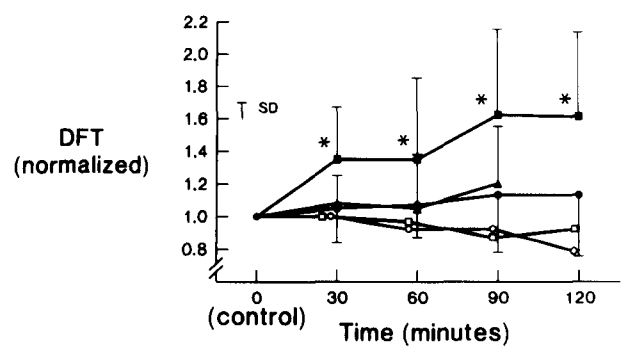


Figure 1. Serum lidocaine concentrations achieved by the three infusion protocols used. **Triangles** = chloralose anesthesia, high dose lidocaine; **circles** = chloralose anesthesia, low dose lidocaine; **squares** = pentobarbital anesthesia, intermediate dose lidocaine.

termediate dose administration) and 16.6 ± 4.9 μg/ml (chloralose anesthesia, high dose lidocaine administration) (Fig. 1). Only two of the six animals given high dose lidocaine completed the full 2 hour protocol; in the four others, the heart could be defibrillated but resuscitation became impossible during the fibrillation-defibrillation sequences while lidocaine was being administered, probably because the serum lidocaine concentration in this group was well into the toxic range.

Pentobarbital-anesthetized dogs. Lidocaine caused the normalized defibrillation threshold to rise significantly in pentobarbital-anesthetized dogs; this effect was seen as early as 30 minutes (Fig. 2). Normalized defibrillation threshold

Figure 2. Effect of lidocaine on defibrillation threshold (DFT) of dogs anesthetized with chloralose or pentobarbital. For comparison, the effect of repeated fibrillation-defibrillation sequences on defibrillation threshold of anesthetized dogs receiving no lidocaine is also shown: **open circles** = chloralose anesthesia, no lidocaine (n = 10) (data from Kerber et al. [13]); **closed circles** = chloralose anesthesia, low dose lidocaine (n = 16); **closed triangles** = chloralose anesthesia, high dose lidocaine (n = 6); **open squares** = pentobarbital anesthesia, no lidocaine (n = 5) (data from Babbs et al. [5]); **closed squares** = pentobarbital anesthesia, intermediate dose lidocaine (n = 9). SD = standard deviation. **Asterisk** indicates $p < 0.05$ versus control.



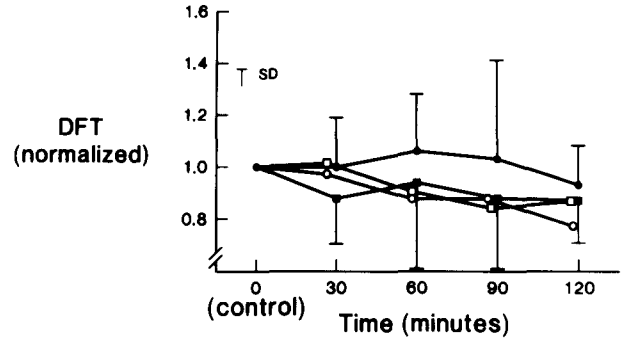


Figure 3. Effect of bretylium on defibrillation threshold (DFT) of dogs anesthetized with chloralose or pentobarbital. For comparison, the effect of repeated fibrillation-defibrillation sequences on defibrillation threshold of anesthetized dogs receiving no bretylium is also shown: **open circles** = chloralose anesthesia, no bretylium (n = 10) (data from Kerber et al. [13]); **closed circles** = chloralose anesthesia, bretylium (n = 10); **open squares** = pentobarbital anesthesia, no bretylium (n = 5) (data from Babbs et al. [5]); **closed squares** = pentobarbital anesthesia, bretylium (n = 10).

reached a maximum of 1.6 ± 0.5 at 90 and 120 minutes of lidocaine infusion. In the two additional pentobarbital-anesthetized dogs that received a low dose lidocaine infusion, the serum lidocaine levels after 30 minutes were 2.2 and 1.2 μg/ml; normalized defibrillation thresholds at that time were 1.2 (20 J increase) and 1.3 (30 J increase).

Chloralose-anesthetized dogs. When lidocaine was administered to chloralose-anesthetized dogs, the normalized defibrillation threshold showed only a lesser rise to 1.2 ± 0.4 (p = NS; Fig. 2). These differing responses of defibrillation threshold to lidocaine, depending on the anesthetic used, were not explained by differing serum lidocaine levels. For example, although the maximal serum lidocaine levels achieved at 90 to 120 minutes in the chloralose-anesthetized, high dose lidocaine group were similar to the serum levels achieved in the pentobarbital-anesthetized group, the defibrillation thresholds rose markedly in the pentobarbital group and only minimally in the chloralose group. The rise of defibrillation threshold in the pentobarbital-anesthetized dogs paralleled the rising serum levels of lidocaine.

Bretylium (Table 2). Twenty dogs received bretylium. The drug caused no significant hemodynamic alterations, although systolic and diastolic blood pressures tended to increase in the pentobarbital-anesthetized dogs that received bretylium. The alterations in actual or normalized (Fig. 3) defibrillation thresholds when bretylium was administered to either chloralose- or pentobarbital-anesthetized dogs did not achieve statistical significance.

Mechanism of Lidocaine-Pentobarbital Interaction

We studied additional dogs in our effort to determine the mechanism of the apparent interaction between lidocaine

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and pentobarbital that resulted in the significant increases in defibrillation thresholds described earlier.

Effects of beta-adrenergic receptor activation and blockade. In two chloralose-anesthetized dogs the mean defibrillation threshold after 1 hour of lidocaine administration was 70 J. With isoproterenol plus lidocaine, heart rate increased from an average of 130 to 175 beats/min and blood pressure changed from 125/95 to 150/82 mm Hg. The mean defibrillation threshold was 60 J. When propranolol was administered in addition to isoproterenol plus lidocaine, heart rate returned to pre-isoproterenol levels (130 beats/min). After isoproterenol was discontinued, heart rate decreased further to 102 beats/min and blood pressure decreased to 90/68 mm Hg and defibrillation threshold fell further with propranolol, to 55 J.

Effects of alpha-adrenergic receptor activation and blockade. In two chloralose-anesthetized dogs the mean defibrillation threshold was 90 J after 1 hour of lidocaine administration and remained unchanged after phenylephrine was added and lidocaine continued. Systolic blood pressure increased from 128 to 187 mm Hg and diastolic blood pressure from 100 to 150 mm Hg. Heart rate decreased from 115 to 98 beats/min.

In six chloralose-anesthetized dogs the mean defibrillation threshold was 107 ± 38 J after 1 hour of lidocaine administration and rose to 121 ± 58 J ($p < 0.05$) after phentolamine was added and lidocaine continued. Five of these six animals showed a rise in defibrillation threshold of 10, 35, 40, 50 and 70 J, respectively, with phentolamine and lidocaine; in one dog defibrillation threshold did not change. Systolic arterial pressure decreased from 144 ± 35 to 112 ± 27 mm Hg with phentolamine and lidocaine ($p < 0.05$) and diastolic pressure decreased from 105 ± 29 to 82 ± 18 mm Hg ($p < 0.05$); heart rate increased from 124 ± 19 to 142 ± 22 beats/min ($p < 0.05$). In contrast, the two pentobarbital-anesthetized dogs that also received lidocaine and phentolamine showed a mean defibrillation threshold energy decrease from 120 to 115 J; systolic pressure decreased from 158 to 120 mm Hg and diastolic pressure from 125 to 95 mm Hg.

Effects of cholinergic stimulation and blockade. In three chloralose-anesthetized dogs the mean defibrillation threshold was 70 J after 1 hour of lidocaine administration and rose to 77 J during bilateral vagal stimulation and continued lidocaine (defibrillation threshold rose in one animal, fell in one and did not change in one). Heart rate decreased in all three dogs from a mean of 133 beats/min to 85 beats/min.

In two chloralose-anesthetized dogs the defibrillation threshold was 90 J after 1 hour of lidocaine administration and did not change after atropine was added and lidocaine continued. Heart rate increased from 82 to 165 beats/min.

Effects of pentobarbital and lidocaine on transthoracic impedance. The control transthoracic impedance in the two dogs averaged 57.5 Ω. After pentobarbital, impedance changed minimally to 56 Ω, a 3% decrease. After the lidocaine bolus and intermediate dose lidocaine, there was

Table 2. Effect of Intravenous Bretylium on Hemodynamics and Defibrillation Threshold

	Control	Bretylium			
		30 Min	60 Min	90 Min	120 Min
A. Chloralose Anesthesia (n = 10)					
Heart rate (beats/min)	185 ± 18	168 ± 30	167 ± 32	167 ± 38	154 ± 28
Systolic arterial pressure (mm Hg)	174 ± 21	163 ± 26	155 ± 22	157 ± 18	158 ± 28
Diastolic arterial pressure (mm Hg)	115 ± 25	107 ± 35	101 ± 20	107 ± 20	109 ± 30
Left ventricular end-diastolic pressure (mm Hg)	8 ± 3	10 ± 4	11 ± 8	13 ± 11	11 ± 5
Defibrillation threshold (J)	60 ± 54	55 ± 41	57 ± 40	54 ± 46	58 ± 52
B. Pentobarbital Anesthesia (n = 10)					
Heart rate (beats/min)	176 ± 16	164 ± 14	158 ± 16	166 ± 18	162 ± 25
Systolic arterial pressure (mm Hg)	150 ± 23	160 ± 30	162 ± 31	174 ± 28	182 ± 25
Diastolic arterial pressure (mm Hg)	104 ± 18	106 ± 22	113 ± 32	123 ± 30	130 ± 19
Left ventricular end-diastolic pressure (mm Hg)	9 ± 5	10 ± 4	10 ± 4	12 ± 4	12 ± 4
Defibrillation threshold (J)	59 ± 31	50 ± 27	50 ± 27	49 ± 25	44 ± 31

a further small decrease to 53.5 Ω, 7% less than the control value.

Discussion

The major findings of this study were: 1) in this experimental model lidocaine increased the transthoracic defibrillation energy requirements but this effect was, in part, anesthesia-related, occurring more noticeably in barbiturate-anesthetized dogs than in chloralose-anesthetized dogs; 2) the increase in defibrillation energy requirements caused by lidocaine paralleled the rising serum levels of this drug in the barbiturate-anesthetized dogs; and 3) bretylium had no significant effect on the energy requirements for transthoracic defibrillation.

Defibrillation threshold. Babbs et al. (4,5) demonstrated that the defibrillation threshold, a measure of the energy requirements for transthoracic defibrillation, was reproducible and that pentobarbital-anesthetized animals had defibrillation energy requirements similar to those of non-anesthetized animals. We (13) have previously confirmed that chloralose-anesthetized animals behave similarly to pentobarbital-anesthetized ones in this regard; with both anesthetic agents, defibrillation threshold tends to gradually decline through repeated fibrillation-defibrillation sequences if no intervention is undertaken (4,13). Data from these studies are shown in Figures 2 and 3 for purposes of comparison with the present study.

Effect of lidocaine on defibrillation threshold. Babbs et al. (1) reported that intravenous lidocaine raised the transthoracic defibrillation threshold by 50 to 100% in pentobarbital-anesthetized dogs. No serum lidocaine levels were obtained in their study. We were able to reproduce the effect of lidocaine on defibrillation energy requirements: lidocaine caused a 60% rise in the transthoracic defibrillation threshold of the pentobarbital-anesthetized dogs we studied. But the effect of lidocaine was much less impressive when administered to chloralose-anesthetized animals, suggesting that the effect is anesthesia-related; in other words, it is in part produced by an interaction between lidocaine and the pentobarbital anesthetic used. This suggestion is reinforced by our observation that the changes in defibrillation threshold were not simply determined by serum lidocaine levels. Levels from low therapeutic to toxic ranges were deliberately achieved in both pentobarbital- and chloralose-anesthetized animals, but the marked rise in defibrillation threshold we saw occurred only in the pentobarbital-anesthetized dogs, even though serum lidocaine levels were comparable or even slightly higher in the chloralose-anesthetized dogs that received high dose lidocaine. On the other hand, the noticeable increase in defibrillation threshold energy requirements between 60 and 90 minutes of lidocaine administration to pentobarbital-anesthetized dogs paralleled the increase in lidocaine infusion rate we selected and the serum lidocaine concentration that was achieved, showing that the effect of the lidocaine was related to the serum lidocaine level achieved in the pentobarbital-anesthetized dogs.

In the pentobarbital-anesthetized dogs the lowest serum lidocaine level was 6.2 ± 1.5 μg/ml at 30 minutes of intermediate dose lidocaine infusion. In humans this would represent a lidocaine level just in the toxic range. Could the pentobarbital-lidocaine effect on defibrillation energy requirements we observed actually represent a toxic effect? In the two pentobarbital-anesthetized dogs that received very low dose lidocaine infusion, the levels achieved were in the very low therapeutic range (1.2 and 2.2 μg/ml); these low levels were associated with small increases in the normalized defibrillation thresholds to 1.3 and 1.2. Furthermore, two of the dogs receiving intermediate dose lidocaine in our study had serum lidocaine levels of 4.3 and 4.2 μg/ml after 30 minutes of infusion, which is a mid therapeutic level in humans. In these two dogs the normalized defibrillation threshold at the corresponding point in the experiment was 1.5 and 1.67, respectively. Thus, lidocaine increased defibrillation energy requirements in pentobarbital-anesthetized dogs at therapeutic levels as well as at toxic levels. A similar relation between lidocaine plasma concentrations and defibrillation energy requirements using an *internal* defibrillation system with a trapezoidal waveform was recently reported by Dorian et al. (14).

Mechanism of lidocaine-barbiturate interaction. We attempted to determine the mechanism of the lidocaine-barbiturate interaction. Acute barbiturate anesthesia has complex cardiovascular effects including alterations in sympathetic tone and parasympathetic tone (9,10). Arterial baroreceptor reflexes are considerably altered. The effects of pentobarbital are also dependent on whether the animal is unused to laboratory procedures and is apprehensive or excited, or both, at the time the anesthetic is given or whether it is trained and calm (9). We evaluated the effects of alpha-adrenergic, beta-adrenergic and cholinergic activation and blockade on defibrillation threshold of chloralose-anesthetized dogs receiving lidocaine. If any of these were the mechanism of the lidocaine-pentobarbital interaction, the defibrillation energy requirements in lidocaine-chloralose dogs receiving these additional manipulations should have increased markedly, mimicking the defibrillation energy requirements of lidocaine-barbiturate–anesthetized dogs. In fact, the addition of the alpha-adrenergic receptor blocking agent phentolamine to lidocaine-chloralose–anesthetized dogs did cause a significant increase in defibrillation requirements, suggesting that at least part of the lidocaine-barbiturate interaction may be due to alpha-adrenergic receptor blockade induced by barbiturate anesthesia. However, the mean increase in defibrillation threshold observed during the phentolamine-lidocaine combination in chloralose-anesthetized dogs was only about 13%, noticeably less than the 50 to 60% increases in defibrillation threshold seen when

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lidocaine was administered to pentobarbital-anesthetized dogs. This suggests that other mechanisms besides alpha-adrenergic receptor blockade may be involved in the lidocaine-barbiturate interaction.

We found a small decrease in transthoracic impedance with pentobarbital and lidocaine of approximately 7%. This modest decrease is consonant with the well known tendency of transthoracic impedance to decrease simply with repeated shocks (4,5,13) and probably does not reflect a specific effect of pentobarbital or lidocaine on impedance. Koo et al. (3) found no effect of bretylium on transthoracic impedance in dogs. In any case, the magnitude of the impedance decrease we found is far too small to explain the marked rise in defibrillation threshold seen in lidocaine-pentobarbital dogs.

One lidocaine metabolite, monoethylglycylxylidide, has significant antiarrhythmic activity (7). The lidocaine assay we used did not measure this metabolite, and we cannot entirely exclude a role for it in the lidocaine effect on defibrillation threshold. However, Halkin et al. (15) showed that only small amounts of this metabolite were present in humans receiving an initial bolus dose of lidocaine followed by a continuous lidocaine infusion for 2 hours, the time period we studied in our animal experiments.

Effect of bretylium on defibrillation threshold. Tacker et al. (2) found that 2 hours after bretylium was administered to pentobarbital-anesthetized dogs the defibrillation threshold had fallen to 80% of control. In our pentobarbital-anesthetized dogs the fall in defibrillation threshold after bretylium was somewhat less (87% of control at 2 hours; p = NS). Our results with chloralose-anesthetized dogs receiving bretylium were similar. Because previous studies (4,5,13) have shown that transthoracic defibrillation threshold falls simply with repeated fibrillation-defibrillation sequences as a result of decreasing transthoracic impedance (Fig. 2 and 3), it appears that bretylium probably had no specific effect on energy requirements for electrical defibrillation; that is, the modest fall in defibrillation threshold we observed during bretylium administration was probably simply an effect of time and multiple defibrillations unrelated to the drug. In the study by Tacker et al. (2), defibrillation threshold fell abruptly immediately after bretylium administration, suggesting a specific effect of the drug, but we could not demonstrate any abrupt change in defibrillation threshold after bretylium (Fig. 3). Our results are consonant with the recent study of Koo et al. (3), who also found no effect of bretylium on defibrillation threshold.

The dose of bretylium we administered is similar to that recommended in humans (16) and is pharmacologically active. We were unable to obtain plasma or myocardial levels of bretylium. The plasma concentration of bretylium has not been correlated with the intensity of its antiarrhythmic action. Myocardial concentrations of bretylium can be far higher than plasma levels and the electrophysiologic and antifibrillatory effects parallel myocardial rather than serum drug kinetics (16,17).

Applications to patients. What is the relevance of these experimental observations to clinical practice? Tacker et al. (2) suggested that elevation of defibrillation threshold by antiarrhythmic drugs such as lidocaine might account for some failures to defibrillate. The pharmacologic effect of lidocaine we observed was small in relation to the interanimal variability, but in an individual subject an elevation of defibrillation energy requirement could cause a defibrillation failure at any given energy. But if the lidocaine effect on defibrillation energy requirements is anesthesia-related it may not occur at all in unanesthetized patients or in patients anesthetized with drugs other than pentobarbital. Two studies in humans have not found a major effect of lidocaine (18,19): we (18) found that there was no difference in the success of defibrillatory shocks given to patients who were or were not receiving intravenous lidocaine. However, although the shocks we administered in that study were of relatively low energy (200 J), no attempt was made to determine an actual threshold energy for defibrillation in the patients receiving lidocaine compared with those who did not receive it. Thus, an effect of lidocaine on defibrillation energy requirements might have been overlooked if the effect was small or if any alteration in energy requirements occurred only at less than 200 J. However, none of the patients in that study were receiving pentobarbital anesthesia at the time of defibrillation.

In another study of open chest defibrillation in patients undergoing coronary artery bypass and other procedures, Babbs et al. (19) specifically looked for but failed to demonstrate an effect of lidocaine on defibrillation energy requirements. Because they used successive shocks of 1, 3, 5, 7, 10 and 20 J it is likely that even a modest effect of lidocaine on defibrillation energy requirements would have been observed. These surgical patients were, of course, anesthetized, but with drugs other than pentobarbital (Guinn GA, personal communication, 1984). Thus, on the basis of our experimental study and the two studies in humans reported, we see no reason to recommend increases in the energy chosen for initial transthoracic shocks for patients with ventricular fibrillation who are receiving lidocaine, especially if they are not simultaneously receiving pentobarbital anesthesia.

Another relevant clinical question concerns the effects of lidocaine on the energy requirements for cardioversion of ventricular tachycardia rather than ventricular fibrillation. Lidocaine is often administered initially to such patients, and electrical cardioversion is then attempted if the arrhythmia persists. Furthermore, such patients are often anesthetized just before cardioversion, frequently with pentobarbital. Lidocaine alone or in combination with pentobarbital might have significant effects on the energy requirements

for cardioversion of ventricular tachycardia in such cases. This question was not addressed in our study.

Whether defibrillation energy requirements are reduced in patients receiving bretylium is at present uncertain. As noted, the energy-reducing effect of bretylium in our study was modest indeed, and could have been accounted for simply by the decrease in transthoracic impedance and defibrillation energy requirements that is known to occur simply from repeated fibrillation-defibrillation episodes (4,5,13). One relevant human study is available: Haynes et al. (20) administered bretylium or lidocaine as initial antiarrhythmic drug therapy to 146 patients with ventricular fibrillation, and then attempted electrical defibrillation. They found no significant difference between the drugs; shocks resulted in defibrillation in 89% of the patients receiving bretylium (average of 2.8 shocks required) and in 93% of the patients receiving lidocaine (average of 2.4 shocks required). It should be noted, however, that the initial and subsequent shock energy levels were high: 320 J. An energy-reducing effect of bretylium might not have been apparent when such high energy levels were selected. Data from low energy defibrillation in patients receiving bretylium are needed to determine whether this drug lowers defibrillation energy requirements in humans.

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